

WHAT IS CLAIMED IS:

1 1. A method of extracting structural information from a NMR data set for
2 a selected macromolecule in an intact biological compartment wherein said selected
3 macromolecule is labeled with an NMR-detectable nucleus, such that said nucleus is present
4 in said macromolecule in an amount greater than is naturally abundant in said
5 macromolecule, said method comprising:

- 6 (a) contacting said cell with radio frequency energy, thereby producing an excited
7 NMR-detectable nucleus;
8 (b) collecting radio frequency data from said excited NMR-detectable nucleus,
9 thereby producing said NMR data set, and
10 (c) analyzing said data set to extract said structural information for said selected
11 macromolecule from said data set.

1 2. The method according to claim 1, wherein said selected
2 macromolecule is overexpressed in said biological compartment.

1 3. The method according to claim 1, wherein said NMR-detectable
2 nucleus is present in an amount detectable by NMR of said biological compartment.

1 4. The method according to claim 1, wherein said selected
2 macromolecule is a member selected from the group consisting of proteins, saccharides,
3 glycoproteins, and nucleic acids.

1 5. The method according to claim 1, wherein said selected
2 macromolecule is in a complex with a small molecule.

1 6. The method according to claim 5, wherein said small molecule is an
2 exogenous small molecule.

1 7. The method according to claim 5, wherein said small molecule is a
2 therapeutic agent or a candidate therapeutic agent.

1 8. The method according to claim 7, wherein said small molecule is an
2 exogenous small molecule.

- 1 **9.** The method according to claim **1**, wherein said macromolecule is
2 further labeled with deuterium.
- 1 **10.** The method according to claim **1**, wherein said biological compartment
2 is present in a suspension.
- 1 **11.** The method according to claim **1**, wherein said structural information
2 is conformational information.
- 1 **12.** The method according to claim **1**, wherein said structural information
2 is for a complex formed between said selected macromolecule and a small molecule selected
3 from therapeutic agents and candidate therapeutic agents.
- 1 **13.** The method according to claim **1**, wherein said structural information
2 is for a complex formed between said selected macromolecule and a member selected from
3 small molecules, endogenous macromolecules and combinations thereof.
- 1 **14.** The method according to claim **1**, wherein said structural information
2 is for a first conformation of said selected macromolecule and a second conformation of said
3 selected macromolecule.
- 1 **15.** The method according to claim **1**, wherein said data set is acquired by
2 a triple resonance NMR method.
- 1 **16.** The method according to claim **15**, wherein said triple resonance NMR
2 experiment is a member selected from HSQC and TROSY.
- 1 **17.** The method according to claim **1**, wherein said biological compartment
2 is prepared by a method comprising:
 - 3 (a) transforming an unlabeled precursor of said labeled biological compartment with
4 a nucleic acid encoding said selected macromolecule, wherein said nucleic
5 acid is operably linked to a promoter non-native to said unlabeled precursor
6 cell, thereby producing a transformed biological compartment;
 - 7 (b) incubating said transformed biological compartment in a medium comprising said
8 NMR-detectable nucleus; and

9 (c) inducing said transformed biological compartment, thereby preparing said labeled
10 biological compartment.

18. The method according to claim 17, further comprising:

(d) inhibiting essentially all transcription in said transformed biological compartment, which is under control of promoters native to said unlabeled precursor biological compartment, while allowing transcription under control of said non-native promoter to proceed.

19. The method according to claim 17, wherein said medium comprises an amino acid labeled with said NMR sensitive nucleus.

20. The method according to claim 17, wherein said medium is deuterated.

21. The method according to claim 17, wherein said biological compartment is a bacterial cell.

22. The method according to claim 17, wherein the non-native promoter encodes an RNA polymerase that is operable during step (d).

23. The method according to claim 17, wherein the non-native promoter is a phage promoter.

24. The method according to claim 18, wherein said inhibiting is caused by administering an inhibitor to said biological compartment in an amount sufficient to cause said inhibiting.

25. The method according to claim 24, wherein said inhibitor is rifampicin

26. The method of claim 1, wherein said selected macromolecule experiences a local viscosity at least 2 fold greater than the viscosity of pure water, wherein said local viscosity and said viscosity of said pure water are determined at the same temperature.

27. The method of claim 1, wherein said selected macromolecule is present in said biological compartment at a weight percent of up to 0.3% compared to the total weight of said biological compartment.

1 **28.** The method of claim 1, wherein said selected macromolecule is
2 present in said biological compartment at a weight percent of up to 50% compared to the total
3 weight of said biological compartment.

1 **29.** The method of claim 1, wherein said selected macromolecule has a
2 molecular weight of at least 5 kDa.

1 **30.** The method of claim 1, wherein said selected macromolecule has a
2 molecular weight of at least 25 kDa.

1 **31.** The method of claim 1, wherein said selected macromolecule has a
2 molecular weight of at least 70 kDa.

1 **32.** The method of claim 1, wherein said biological compartment is a
2 living cell.

1 **33.** The method of claim 1, wherein said biological compartment is a cell
2 that has been metabolically arrested.

1 **34.** The method of claim 1, wherein said selected macromolecule is
2 expressed from a plasmid.

1 **35.** The method of claim 1, using a multidimensional multinuclear method.

1 **36.** The method of claim 35, using an HNCA experiment.

1 **37.** The method of claim 35, using an HMQC experiment.

1 **38.** The method of claim 1, wherein said compartment is a biological cell.

1 **39.** The method of claim 38, wherein said cell is a prokaryotic cell.

1 **40.** The method of claim 39, wherein said cell is a *E. coli* cell.

1 **41.** The method of claim 38, wherein said cell is a eukaryotic cell.

1 **42.** The method of claim 41, wherein said cell is a yeast cell.

1 **43.** The method of claim 41, wherein said cell is a mammalian cell.

1 **44.** The method of claim 43, wherein said cell is a human cell.

1 **45.** A method of extracting structural information from a NMR data set for
2 a selected macromolecule of an intact biological compartment wherein said selected
3 macromolecule is labeled with a NMR-detectable nucleus, such that said nucleus is present in
4 said macromolecule in an amount greater than is naturally abundant in said macromolecule,
5 wherein said nucleus is not ^{19}F , said method comprising:

- 6 (a) contacting said biological compartment with radio frequency energy,
7 thereby producing an excited NMR-detectable nucleus, and
8 (b) collecting radio frequency data from said excited NMR-detectable
9 nucleus, thereby producing said NMR data set.

1 **46.** The method according to claim 45, wherein said selected
2 macromolecule is overexpressed in said biological compartment.

1 **47.** The method according to claim 45, wherein said NMR-detectable
2 nucleus is present in an amount detectable by NMR of said intact, biological compartment.

1 **48.** The method according to claim 45, wherein said selected
2 macromolecule is a member selected from the group consisting of proteins, saccharides,
3 glycoproteins, and nucleic acids.

1 **49.** The method according to claim 45, wherein said selected
2 macromolecule is in a complex with a small molecule.

1 **50.** The method according to claim 49, wherein said small molecule is an
2 exogenous small molecule.

1 **51.** The method according to claim 49, wherein said small molecule is a
2 therapeutic agent or a candidate therapeutic agent.

1 **52.** The method according to claim 51, wherein said small molecule is an
2 exogenous small molecule.

1 **53.** The method according to claim 45, wherein said macromolecule is
2 further labeled with deuterium.

1 **54.** The method according to claim 45, wherein said biological
2 compartment is present in a suspension.

1 **55.** The method according to claim 45, wherein said structural information
2 is conformational information.

1 **56.** The method according to claim 45, wherein said structural information
2 is for a complex formed between said selected macromolecule and a small molecule selected
3 from therapeutic agents and candidate therapeutic agents.

1 **57.** The method according to claim 45, wherein said structural information
2 is for a complex formed between said selected macromolecule and a member selected from
3 small molecules, endogenous macromolecules and combinations thereof.

1 **58.** The method according to claim 45, wherein said structural information
2 is for a first conformation of said selected macromolecule and a second conformation of said
3 selected macromolecule.

1 **59.** The method according to claim 45, wherein said data set is acquired by
2 a triple resonance NMR method.

1 **60.** The method according to claim 59, wherein said triple resonance NMR
2 experiment is a member selected from HSQC and TROSY.

1 **61.** The method according to claim 45, wherein said biological
2 compartment is prepared by a method comprising:

3 (a) transforming an unlabeled precursor of said labeled biological compartment with
4 a nucleic acid encoding said selected macromolecule, wherein said nucleic
5 acid is operably linked to a promoter non-native to said unlabeled precursor
6 biological compartment, thereby producing a transformed biological
7 compartment;

8 (b) incubating said transformed biological compartment in a medium comprising said
9 NMR-detectable nucleus; and

10 (c) inducing said transformed biological compartment, thereby preparing said labeled
11 biological compartment.

1 **62.** The method according to claim **61**, further comprising:
2 (d) inhibiting essentially all transcription in said transformed biological compartment,
3 which is under control of promoters native to said unlabeled precursor
4 biological compartment, while allowing transcription under control of said
5 non-native promoter to proceed.

1 **63.** The method according to claim **61**, wherein said medium comprises an
2 amino acid labeled with said NMR sensitive nucleus.

1 **64.** The method according to claim **61**, wherein said medium is deuterated.

1 **65.** The method according to claim **61**, wherein said biological
2 compartment is a bacterial cell.

1 **66.** The method according to claim **61**, wherein the non-native promoter
2 encodes an RNA polymerase that is operable during step (d).

1 **67.** The method according to claim **61**, wherein the non-native promoter is
2 a phage promoter.

1 **68.** The method according to claim **62**, wherein said inhibiting is caused by
2 administering an inhibitor to said biological compartment in an amount sufficient to cause
3 said inhibiting.

1 **69.** The method according to claim **68**, wherein said inhibitor is rifampicin.

1 **70.** The method of claim **45**, wherein said selected macromolecule
2 experiences a local viscosity at least 2 fold greater than the viscosity of pure water, wherein
3 said local viscosity and said viscosity of said pure water are determined at the same
4 temperature.

1 **71.** The method of claim **45**, wherein said selected macromolecule is
2 present in said biological compartment at a weight percent of up to 0.3% compared to the
3 total weight of said biological compartment.

1 **72.** The method of claim **45**, wherein said selected macromolecule is
2 present in said biological compartment at a weight percent of up to 50% compared to the total
3 weight of said biological compartment.

1 **73.** The method of claim **45**, wherein said selected macromolecule has a
2 molecular weight of at least 5 kDa.

1 **74.** The method of claim **45**, wherein said selected macromolecule has a
2 molecular weight of at least 25 kDa.

1 **75.** The method of claim **45**, wherein said selected macromolecule has a
2 molecular weight of at least 70 kDa.

1 **76.** The method of claim **45**, wherein said biological compartment is a
2 living cell.

1 **77.** The method of claim **45**, wherein said biological compartment is a cell
2 that has been metabolically arrested.

1 **78.** The method of claim **45**, wherein said selected macromolecule is
2 expressed from a plasmid.

1 **79.** The method of claim **45**, using a multidimensional multinuclear
2 method.

1 **80.** The method of claim **79**, using an HNCA experiment.

1 **81.** The method of claim **79**, using an HMQC experiment.

1 **82.** The method of claim **45**, wherein said compartment is a biological cell.

1 **83.** The method of claim **82**, wherein said cell is a prokaryotic cell.

1 **84.** The method of claim **83**, wherein said cell is a *E. coli* cell.

1 **85.** The method of claim **83**, wherein said cell is a eukaryotic cell.

1 **86.** The method of claim **85**, wherein said cell is a yeast cell.

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87. The method of claim 85, wherein said e cell is a mammalian cell.
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88. The method of claim 87, wherein said cell is a human cell.

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